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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides
and
Toxic Substances

DATE: March 22, 2007

TXR# 0054534

MEMORANDUM

SUBJECT: **Iprodione**: Reconsideration of Linear Extrapolation on Leydig Cell Tumor for Cancer Risk Assessment. DB Barcode D337827.

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PC Code: 109801

The registrant [Bayer CropScience] submitted mechanistic data for male rat Leydig cell tumors in support of their position that the current use of a linear low-dose extrapolation model to define the carcinogenic potential of iprodione to induce Leydig cell tumors is overly conservative and inappropriate. These data were discussed by members of an *ad hoc* peer review committee in the fall of 2005, and it was concluded that the data did not provide a sufficient basis for establishing the mode of action for iprodione as hypothesized by the registrant; *i.e.*, decreased testosterone, increased LH and cell proliferation.

In March, 2006, the registrant presented a summary of their previously-submitted proposed mechanism data for Leydig cell tumors to the Iprodione risk assessment team, HED Senior Science Advisors, and researchers from ORD. Based on current understanding of endocrine and paracrine control of Leydig cell function, HED informed Bayer that it was reconsidering the issue of linear extrapolation on this tumor for cancer risk assessment.

Based on our internal discussions, as proposed in the Draft Guidance on the Cancer Hazard Assessment of Pesticides that Induce Leydig Cell Tumors in Rats, pesticides that induce Leydig cell tumors (LCTs) in rodents should be classified as follows:

A. "Not likely to be carcinogenic to humans at levels that do not alter rat hormone homeostasis"

if they meet the following criteria:

(i) Acceptable data are available to indicate a non-mutagenic mode of action
(ii) Acceptable data are available that meet the evidence that the mode of action is through altered testosterone and/or LH levels.
(iii) Perturbation of hormone homeostasis is not anticipated at levels of human exposure.

In these instances, an upper bound estimate (Q*) should not be derived, and the most sensitive toxicity endpoint in the chemical database should be used to establish Reference Doses (RfDs) and Margins of Exposure (MOEs).

B. "Suggestive Evidence of Carcinogenic Potential"

When the hormonally-mediated pathway is biologically plausible, but there are insufficient data to support the proposed MOA and its key events, *if they meet the following criteria*:

(i) Acceptable data are available to indicate a non-mutagenic mode of action
(ii) A treatment related increase in testicular tumor incidence observed in a single species (usually rats)
(iii) No other treatment-related tumors seen

In cases where a pesticide induces both LCTs and tumors at other sites, as in the case of iprodione, the LCTs should be used as part of the weight of evidence for evaluating potential human cancer hazard and ***not*** **as the basis of a linear low dose extrapolation**.

CONCLUSION: It is concluded that the cancer classification of iprodione remains as a "Likely" human carcinogen, based on the increased incidence of liver tumors in both sexes of the mouse and the increased incidence of Leydig cell tumors in male rats; however, the Leydig cell tumor Q* will no longer be used as the basis of the linear low dose extrapolation.

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Chemical: Iprodione

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